

Illumina's assays do *not* indicate the relative strength of binding

Court's Construction

12. The phrase "indicating an extent of hybridization," as used in the claims of U.S. Patent No. 5,795,716, means "indicating the relative strength of binding;"

Markman Order at ¶12

'716 Patent Claim 1

What is claimed is:

1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:
computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;
computer code that performs a comparison of said plurality of probe intensities to each other;
computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes; and
a computer readable medium that stores said computer codes.

'716 Patent col. 41:59-67; 42:59-67

- Illumina's assays — perfect match and mismatch have *indistinguishable* strength of binding
- Illumina's assay intensities indicate the extent of enzymatic reaction, *not* relative strength of binding

End-base mismatches do *not* typically show different strength in binding

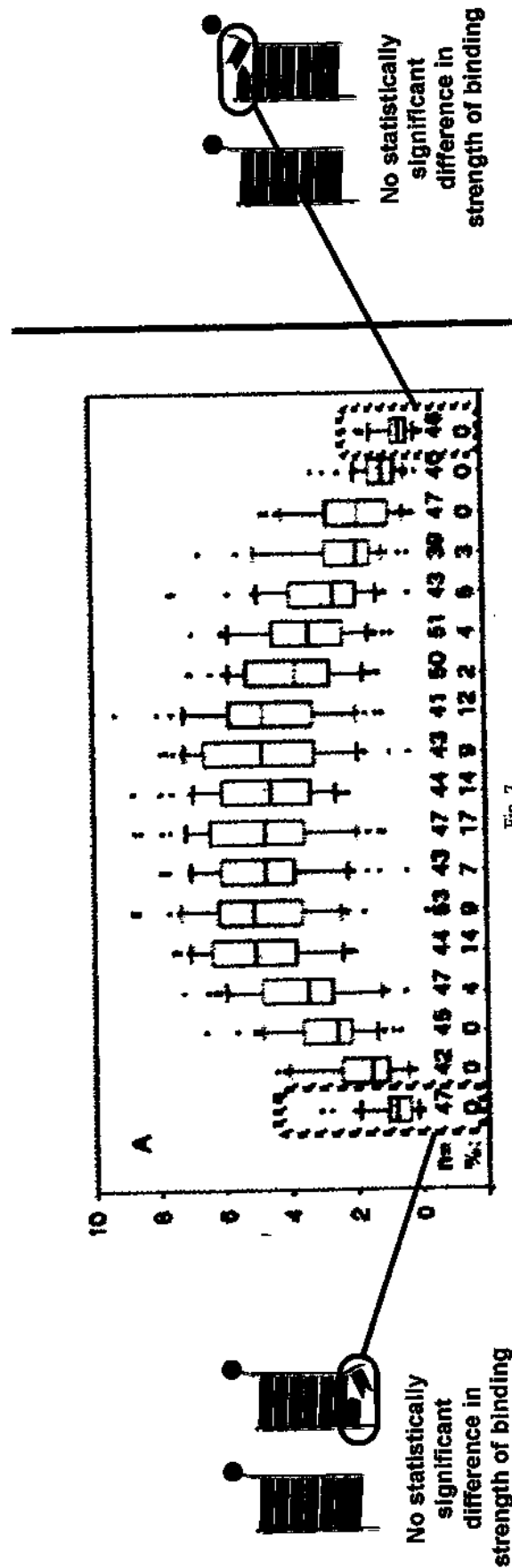


Fig. 7

Wick, L.M. et al. "On-chip nonequilibrium dissociation curves and dissociation rate constants as methods to assess specificity of oligonucleotide probes," 2006, Nucleic Acids Research 34(3): e26

- Conditions must be optimized to detect any difference in strength of binding
- End mismatch has little to no effect on strength of binding, even for short probes
- Illumina's assays are designed to do the opposite — longer probes and conditions set to avoid any differences in strength of binding

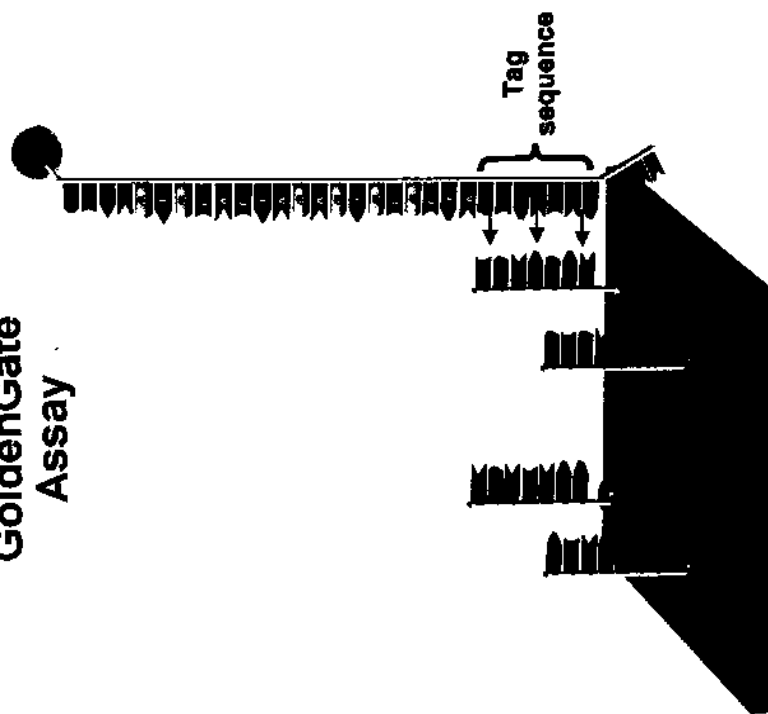
GoldenGate intensities do not "indicate an extent of hybridization" as required by claim 1

'716 Patent Claim 1

What is claimed is:

1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:
computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;
computer code that performs a comparison of said plurality of probe intensities to each other;
computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes; and
a computer readable medium that stores said computer codes.

GoldenGate Assay



Tag has exact same sequence for match or mismatch (*i.e.*, no difference in strength of binding)

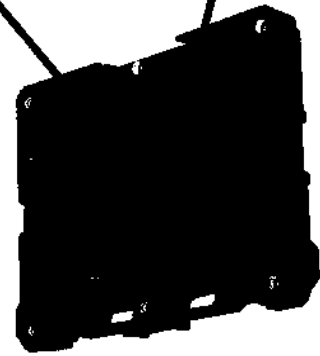
Array Matrix Not A "Biological Chip Plate"

'531 Patent Specification

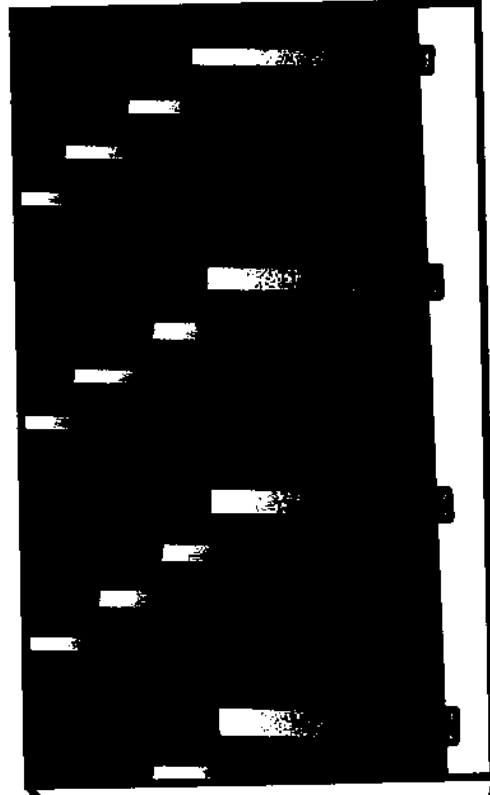
G. Biological Chip Plate: A device having an array of biological chips in which the probe array of each chip is separated from the probe array of other chips by a physical barrier resistant to the passage of liquids and forming an area or space, referred to as a "test well," capable of containing liquids in contact with the probe array.

'531 Patent col. 4:19-25

**NO separate
"biological chips"
on a plate**



**Array Matrix
underside**



BeadChip Not A "Biological Chip Plate"

'531 Patent Specification

G. Biological Chip Plate: A device having an array of biological chips in which the probe array of each chip is separated from the probe array of other chips by a physical barrier resistant to the passage of liquids and forming an area or space, referred to as a "test well," capable of containing liquids in contact with the probe array.

'531 Patent col. 4:19-25

**NO separate
"biological chips"
on a plate**



BeadChip

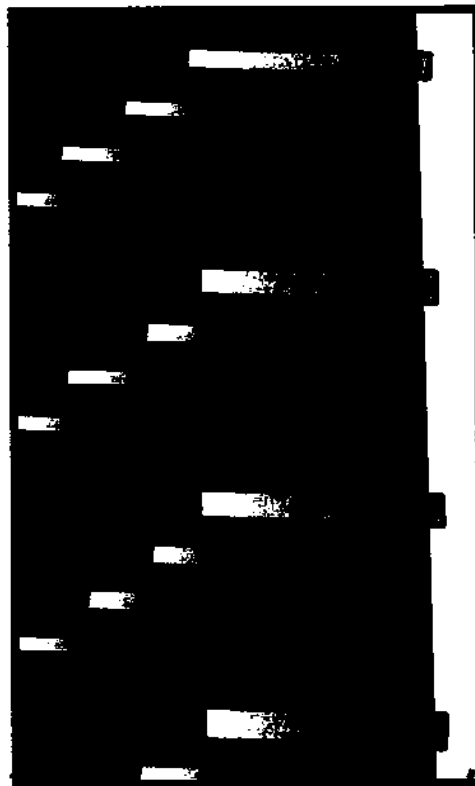
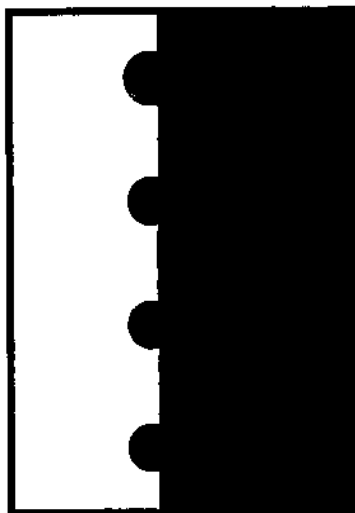
Illumina's Array Matrix Does Not Have A "Wafer"

'531 Patent, Claim 1

1. A method for making a biological chip plate comprising the steps of:

- * * *
- (b) providing a wafer comprising on its surface a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different, arranged in a specially defined and physically addressable manner;

Claim 1, '531 Patent, col. 12:41-49



Array Matrix
topside



Array Matrix
underside

Illumina's Products Do Not Meet The Attaching Step According To Affymetrix's Own Expert

Affymetrix's Expert Report

43. Additionally, neither of the Chetverin references describes a method for "attaching the wafer to the body so that the probe arrays are exposed to the spaces of the wells," as required by claims 1 and 2 or "applying a material resistant to the flow of the liquid sample so as to surround the probe arrays, thereby creating test wells" as required by claims 3 and 4.

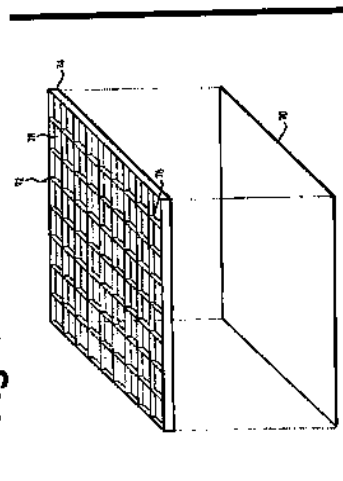
Felder Report at ¶ 43

Chetverin '463 Patent

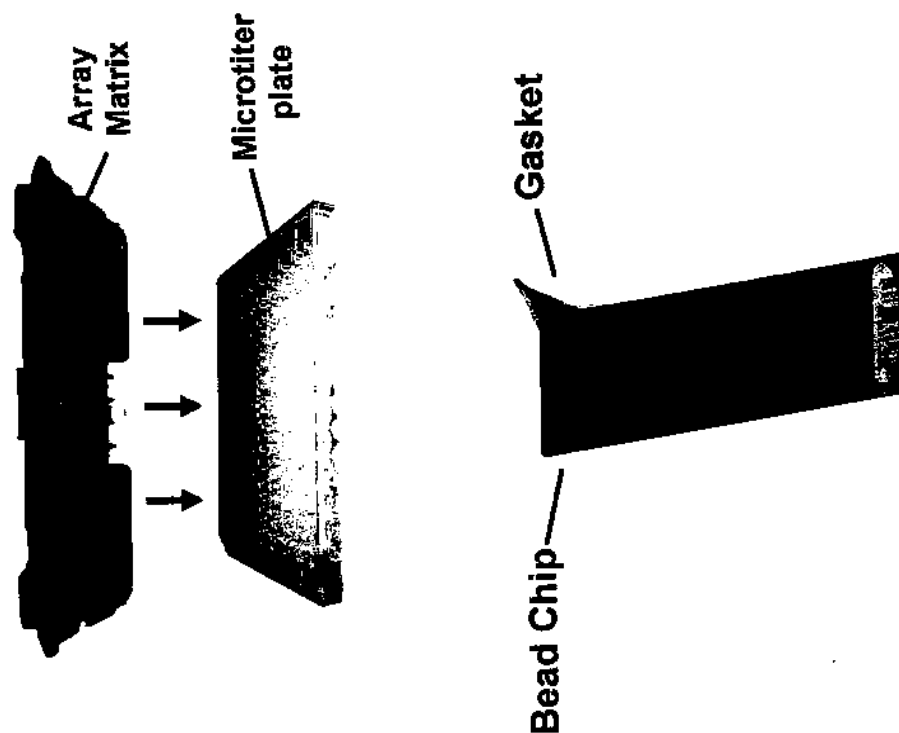
The sectioned array can also be created by applying a lattice to the solid support and bonding it to the surface so that each area is surrounded by impermeable walls. The technique of application of the lattice to the support is not critical; such means are well known in the art and include using adhesives and heat bonding.

'463 Patent at col. 10:28-34

Fig. 3 of '463 Patent

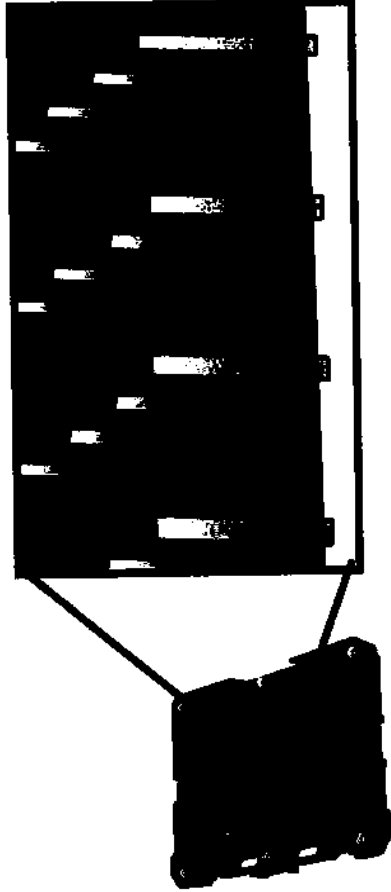


Illumina's Products -- NO "attaching"

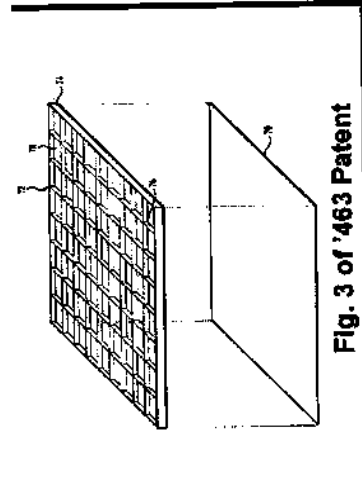


Illumina Does Not Infringe The '531 Patent

- Not a biological chip plate
- No wafer with probes on its surface
- No attachment of accused "wafer" to body by Affymetrix's own expert



Array Matrix underside



"Encoding System" As Defined By The Court

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AFFYMETRIX, INC.,
Plaintiff,
v.
ILLUMINA, INC.,
Defendant.
Civil Action No. 04-901 JJP

ORDER

1. The phrase "said beads being coded with an encoding system," as used in the claims of U.S. Patent No. 6,355,432, means "said beads having a property associated with each bead that can be used to distinguish one bead from another;"

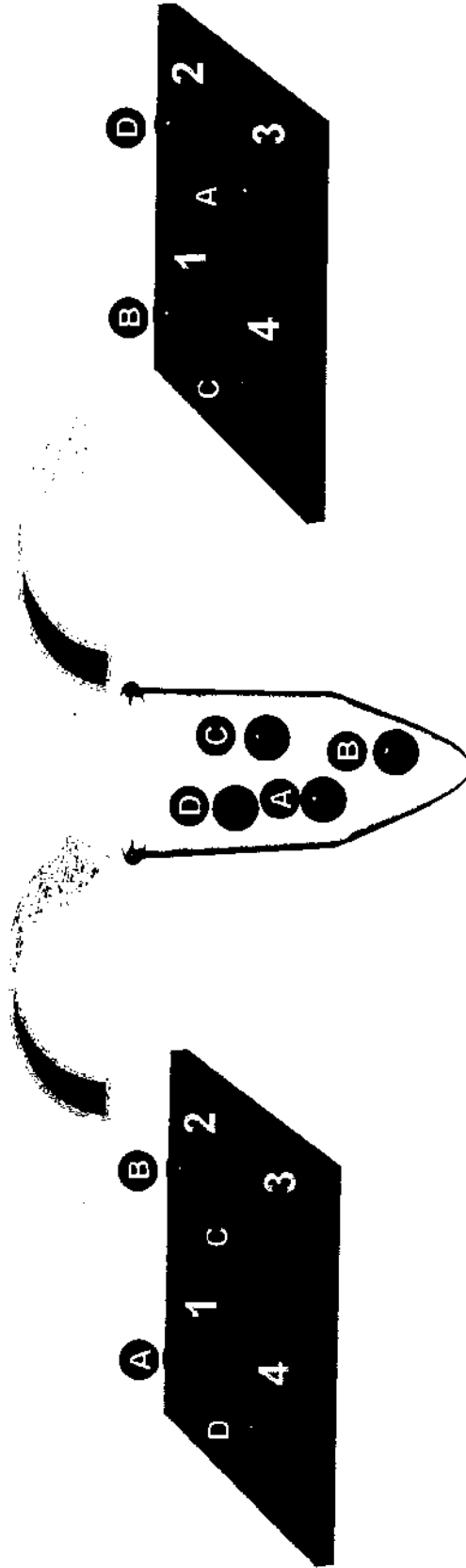
property associated
with the bead

separate from the
binding polymer

2. The term "target specific sequence," as used in the claims of U.S. Patent No. 6,355,432, means "a known polymer sequence that has affinity for another sequence;"

3. The term "substrate," as used in the claims of U.S. Patent No. 6,646,243, means "a material having a rigid or semi-rigid surface;"

The Accused Spatial Location "Map" Is Not A Property Of The Bead



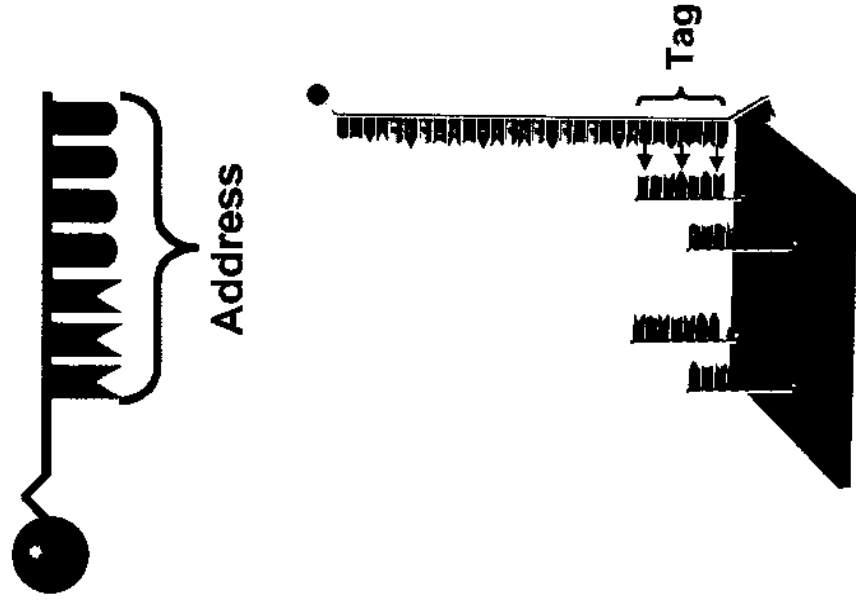
Bead	Location
A	3
B	1
C	4
D	2

Bead	Location
A	1
B	2
C	3
D	4

Location is not constant

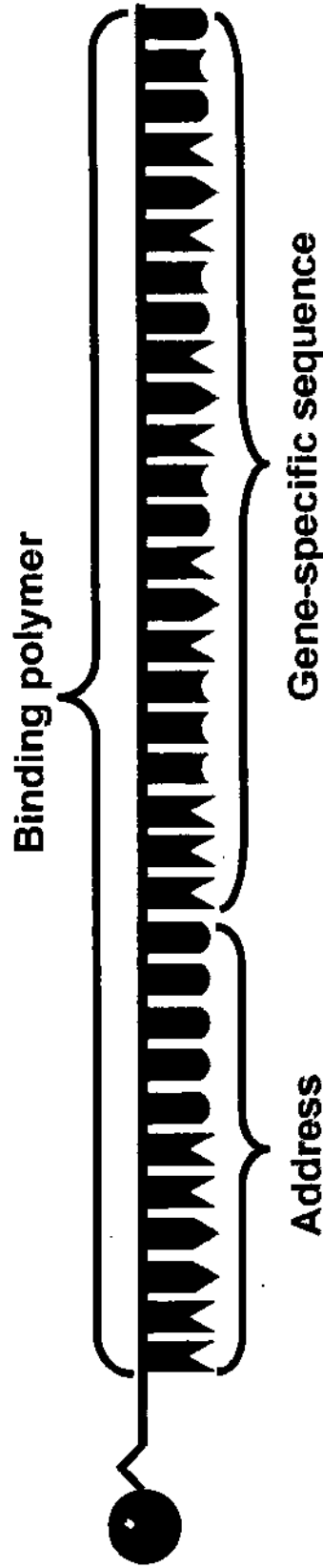
Illumina's Beads Have No "Encoding System" Separate From The Binding Polymer

- Golden Gate/DASL bead address is NOT separate from the binding polymer
- Address has two functions:
 - 1) capture assay products
 - 2) used to decode array in manufacturing



Illumina's Beads Have No "Encoding System" Separate From The Binding Polymer

Infinium/Direct Hyb bead address is part of the binding polymer, NOT separate from it

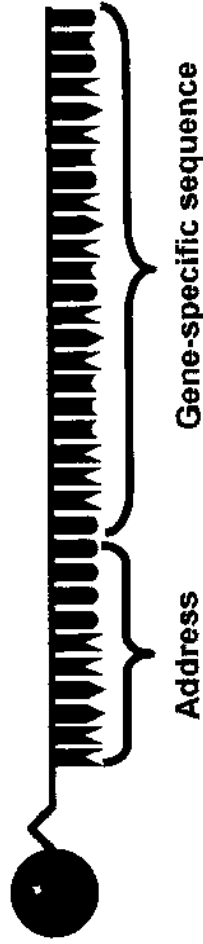


DNA on bead serves two functions:

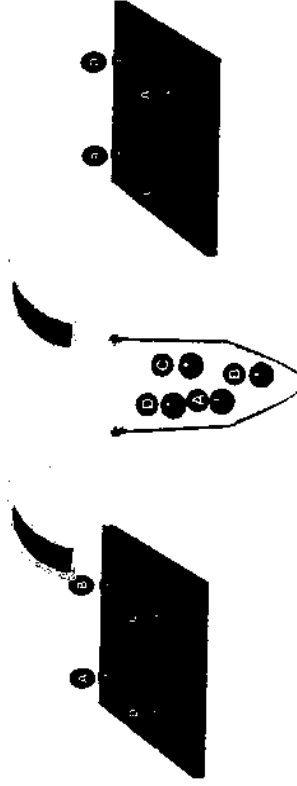
- capture gene-specific sequences
- used for decoding in manufacturing

'432 Patent Claims 2 And 9 Not Infringed Because No "Encoding System"

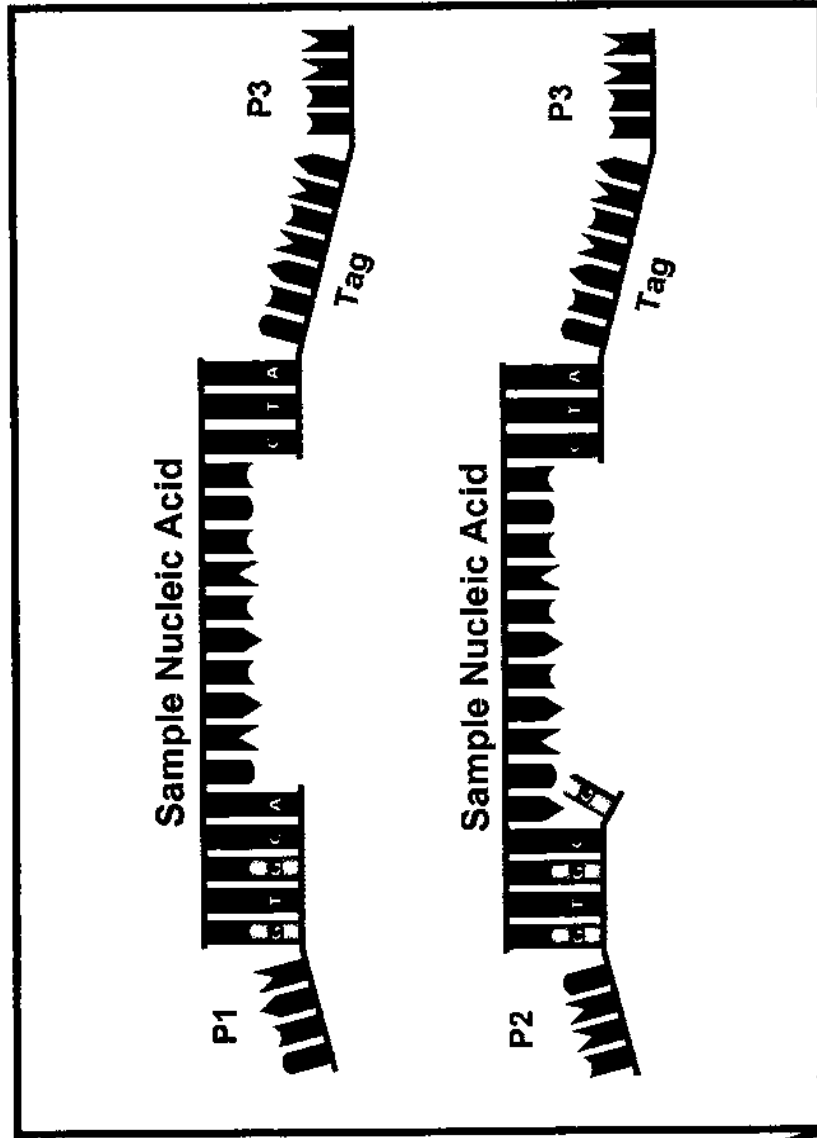
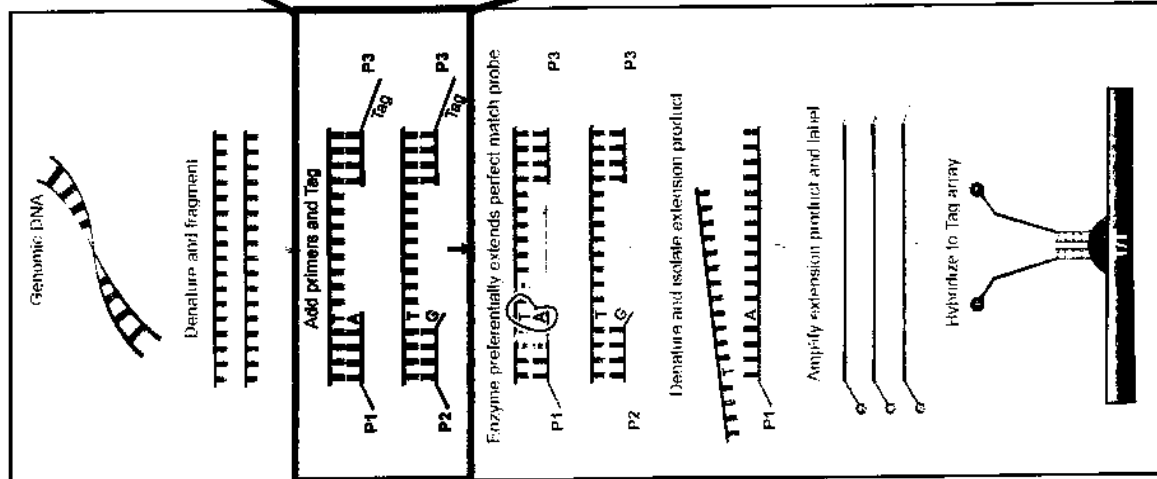
- Address of the Infinium/
Direct Hyb assay beads
are *not separate from*
binding polymer



- Spatial location is *NOT a property associated with each bead* so it is not an "encoding system" under the Court's construction

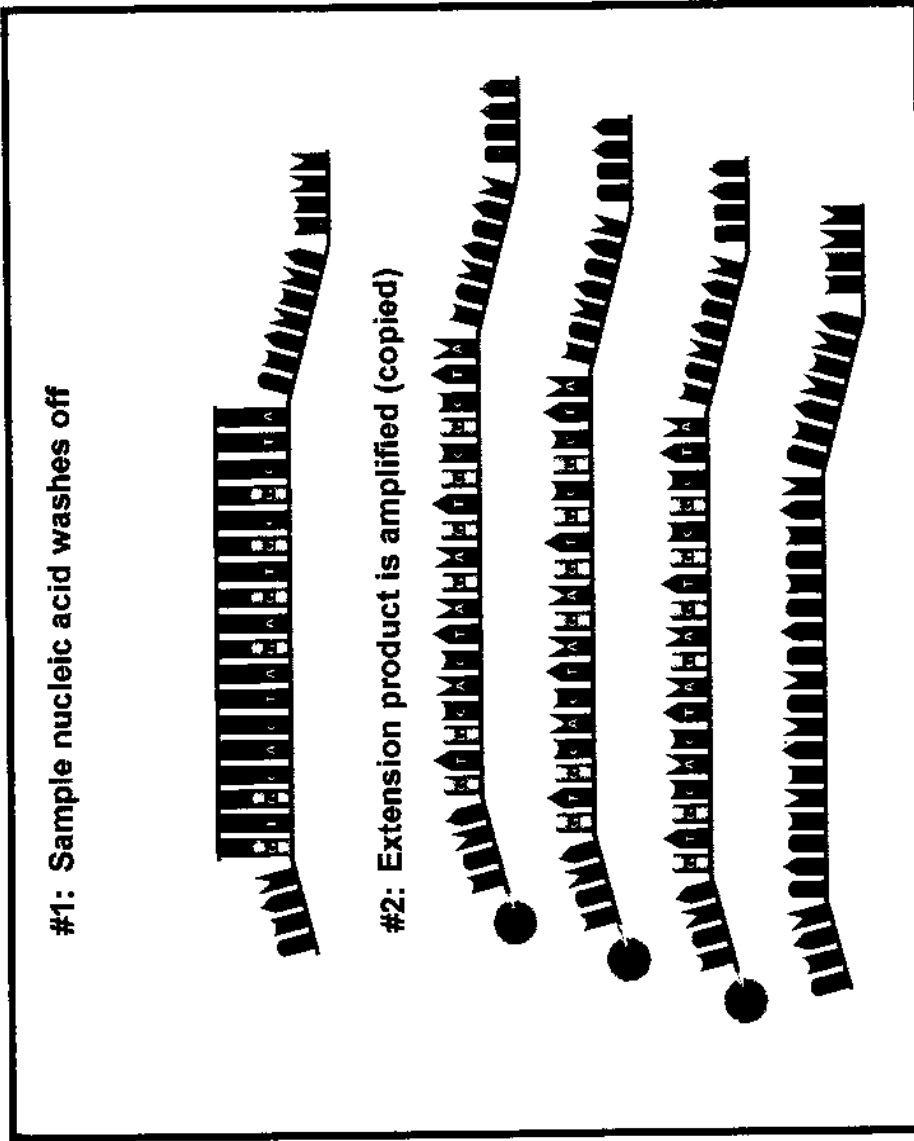
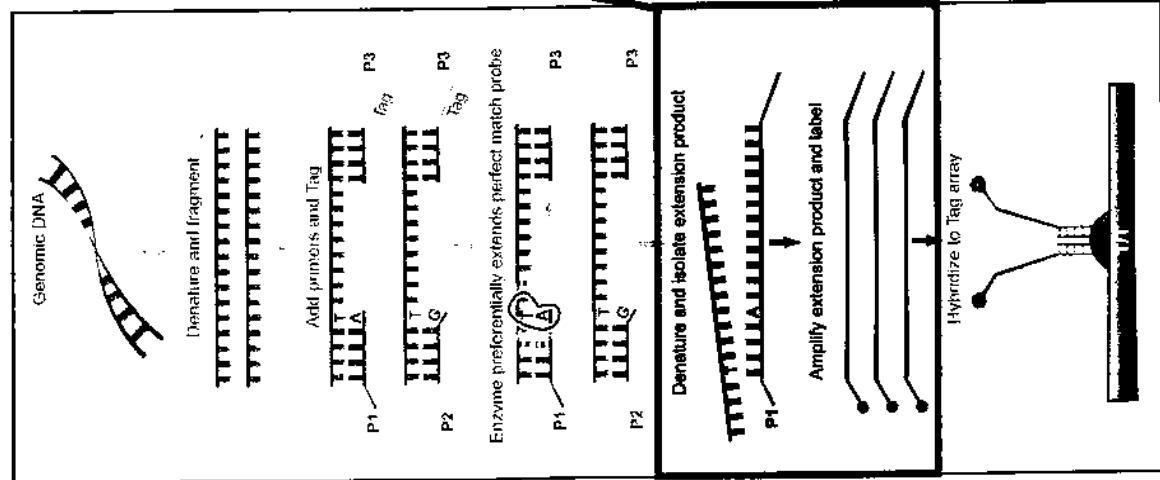


Illumina's GoldenGate Assay: Step 1



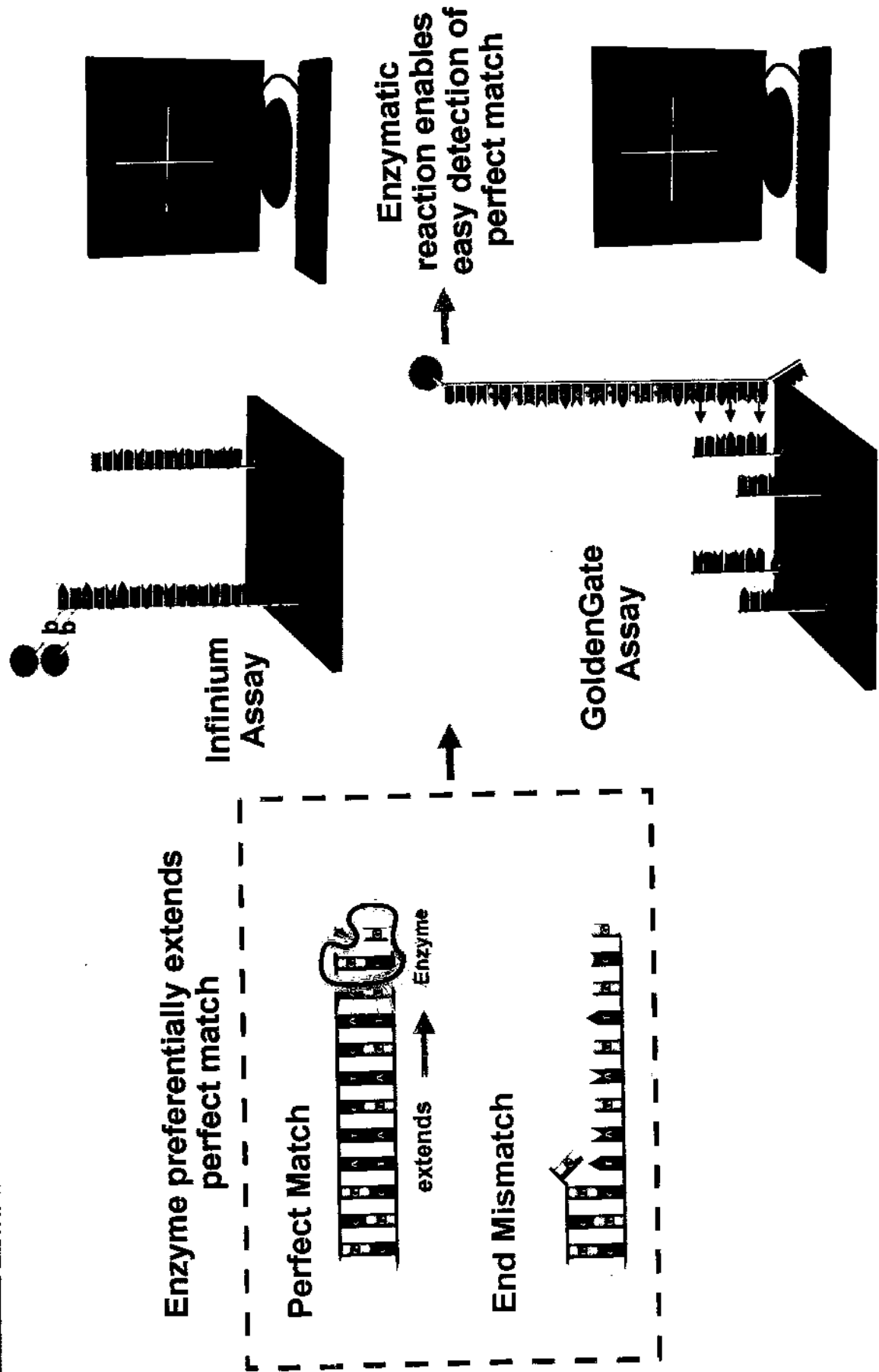
- Probes with P1 & P2 added to bind with sample nucleic acid adjacent to unknown base
- Locus specific nucleic acid with Tag sequence and P3 binds to downstream part of sample nucleic acid

Illumina's GoldenGate Assay: Step 3



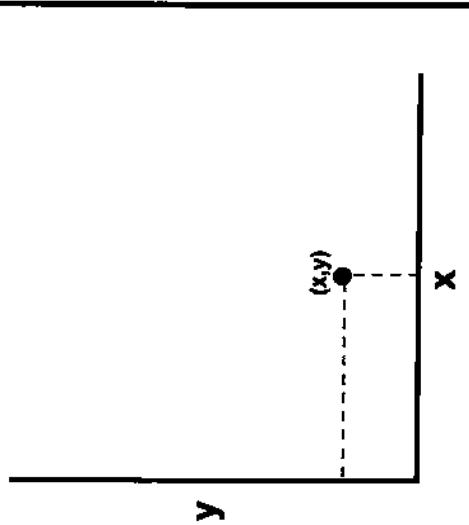
- Sample nucleic acid is separated from extension product and washed off
- Extension product is amplified (copied) and labeled

Illumina's Enzyme-Based Assays

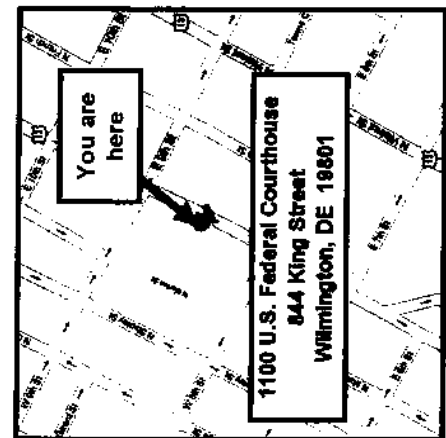


GenCall Polar Transformation: Like Transforming Your Address Into Latitude/Longitude

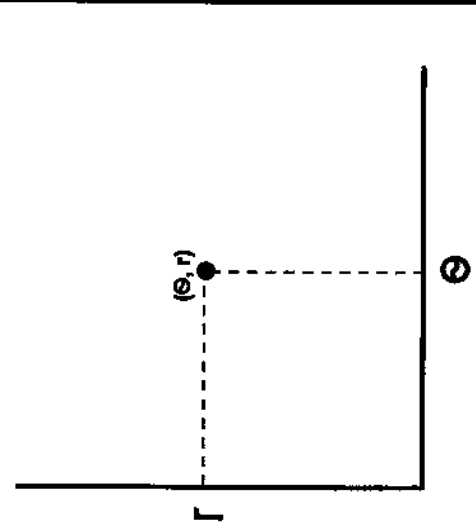
GENCALL CARTESIAN GRAPH



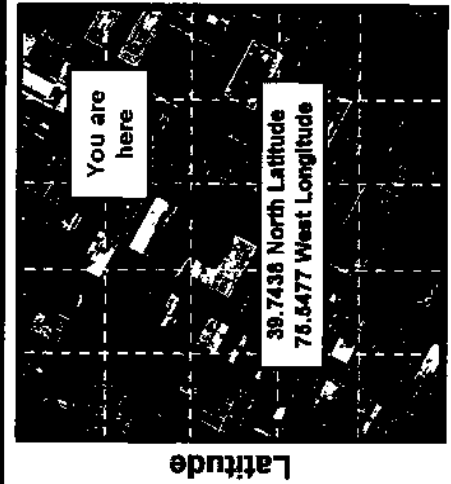
DOWNTOWN WILMINGTON, DE



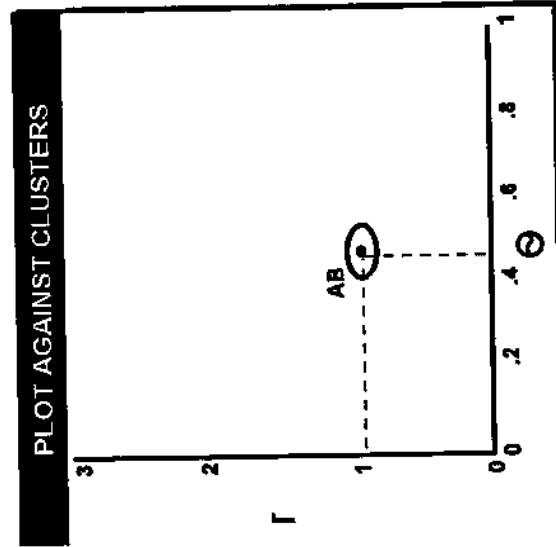
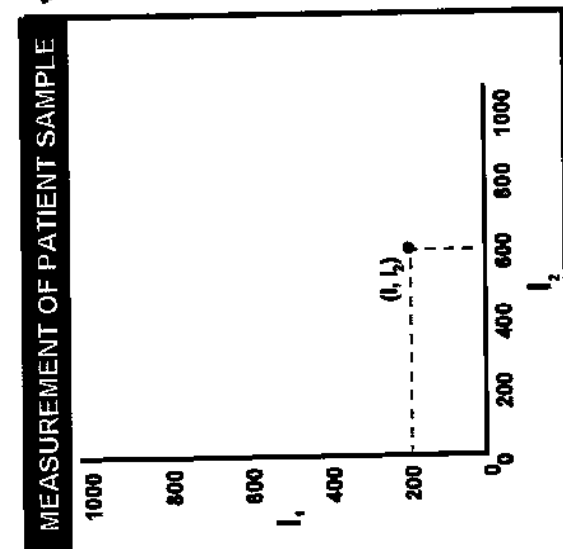
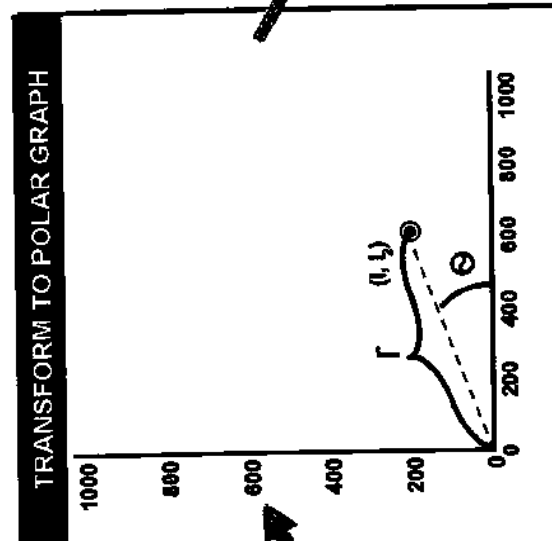
GENCALL POLAR GRAPH



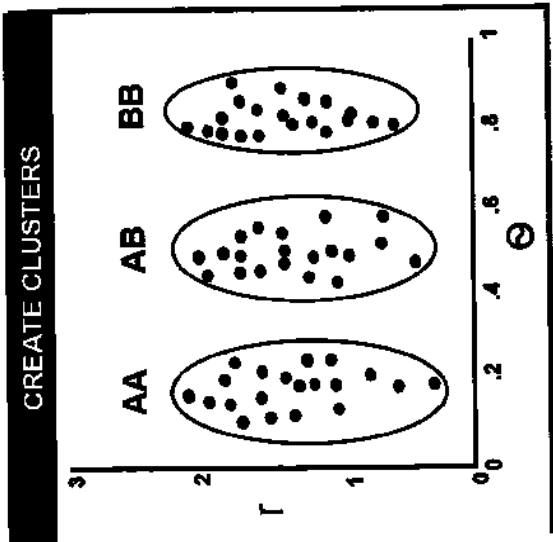
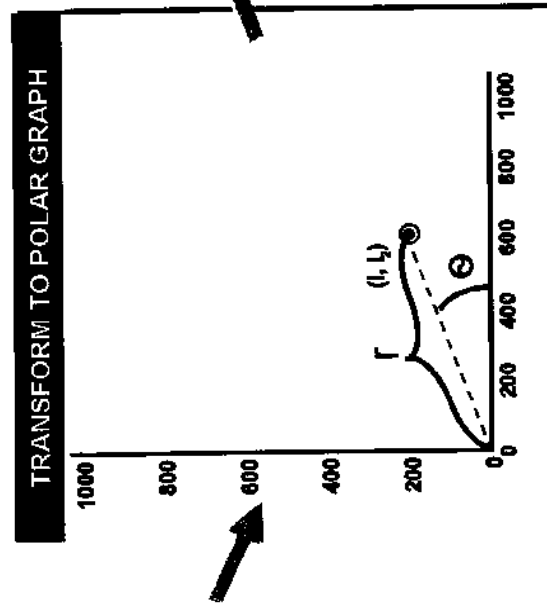
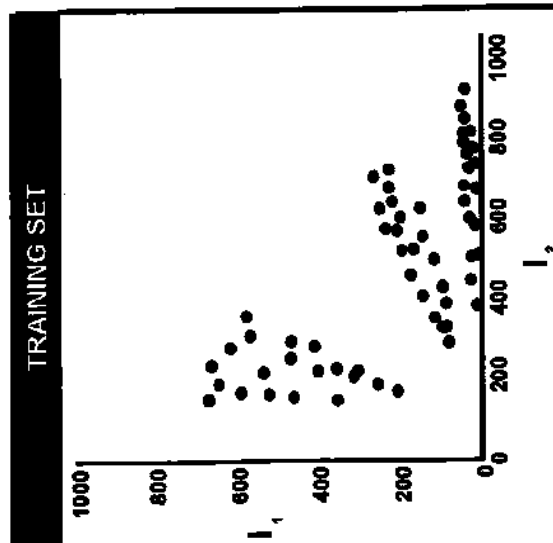
COURTHOUSE



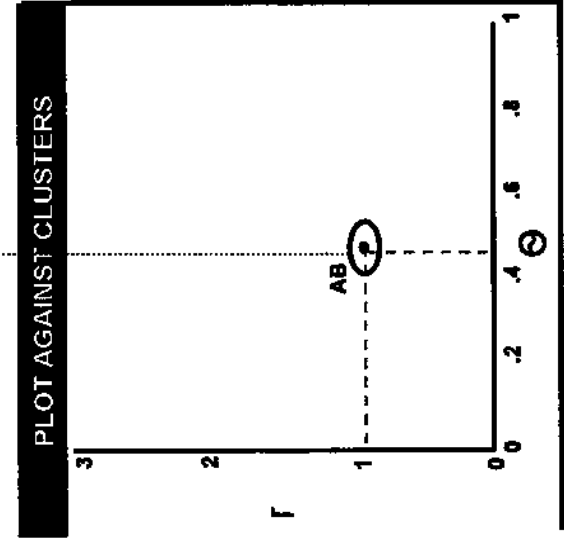
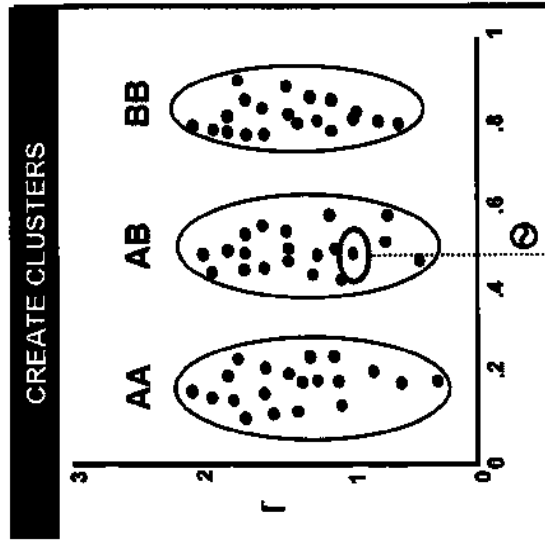
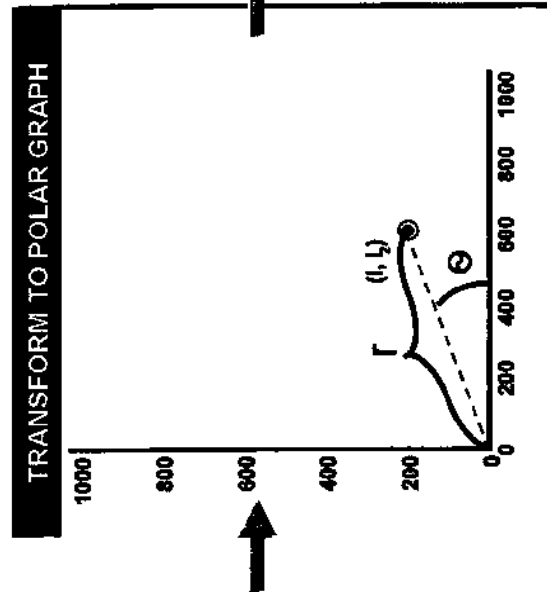
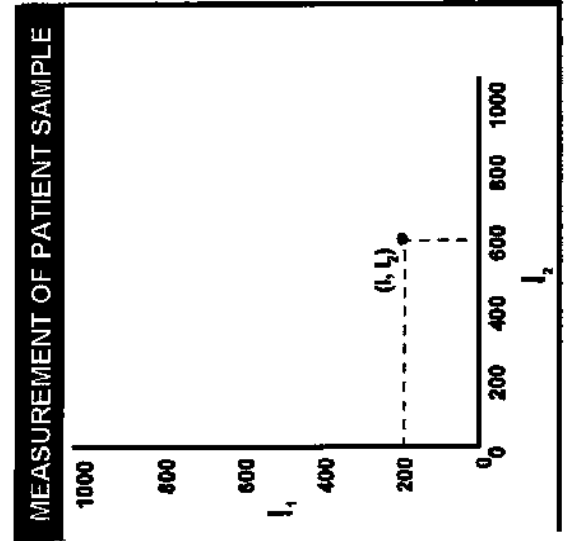
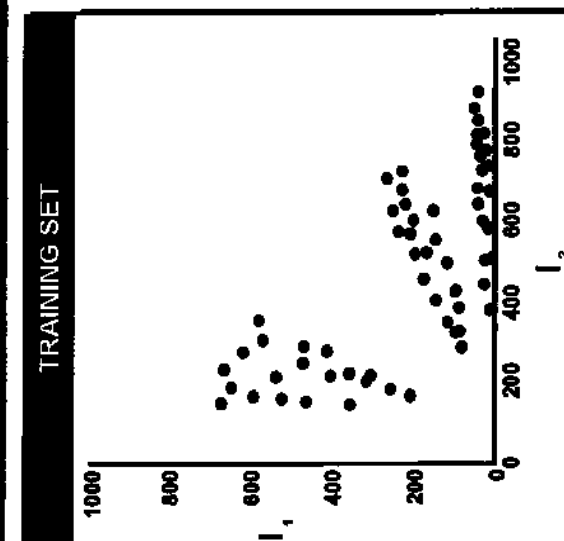
Illumina makes genotyping calls through transformation and clustering



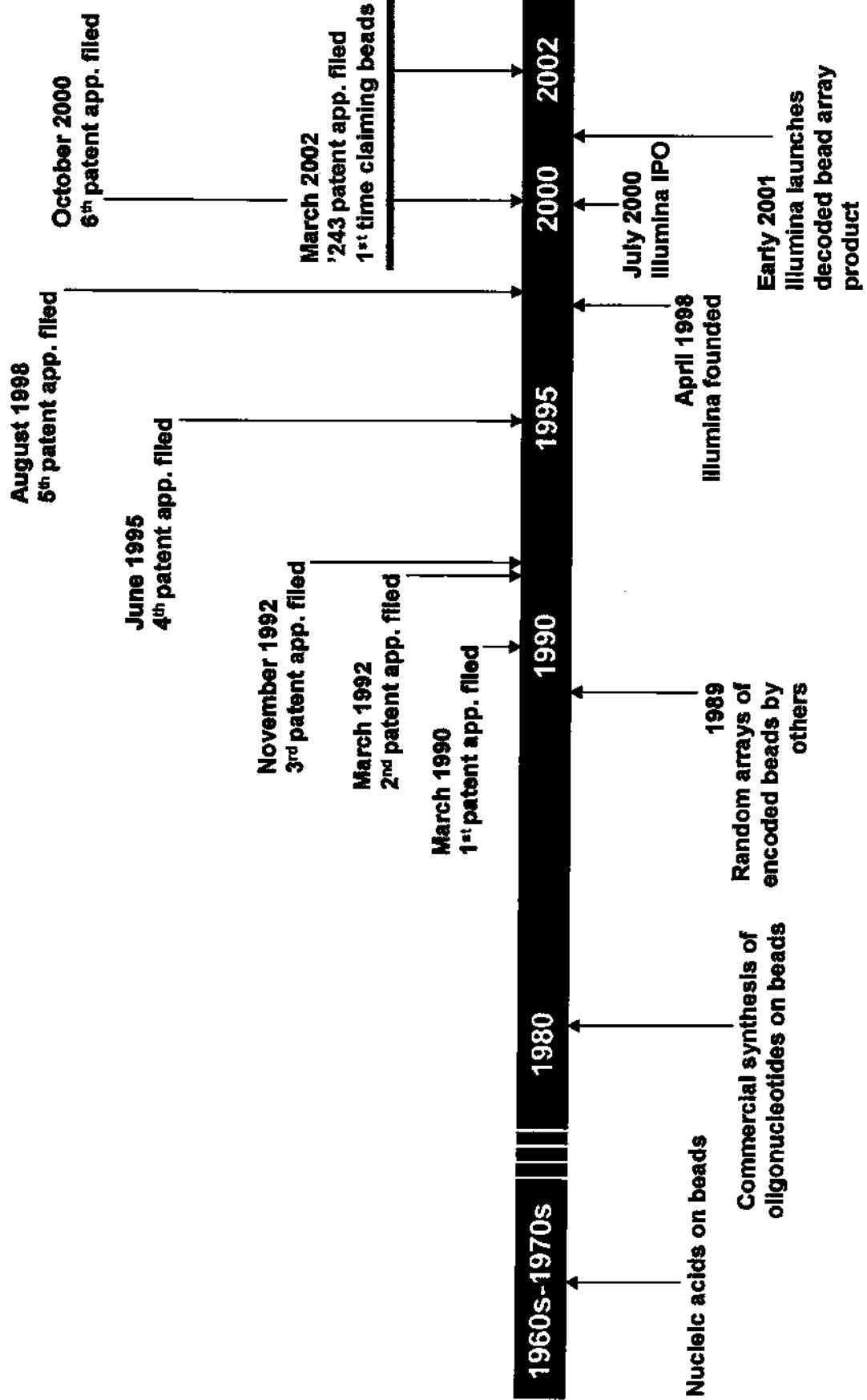
Illumina makes genotyping calls through transformation and clustering



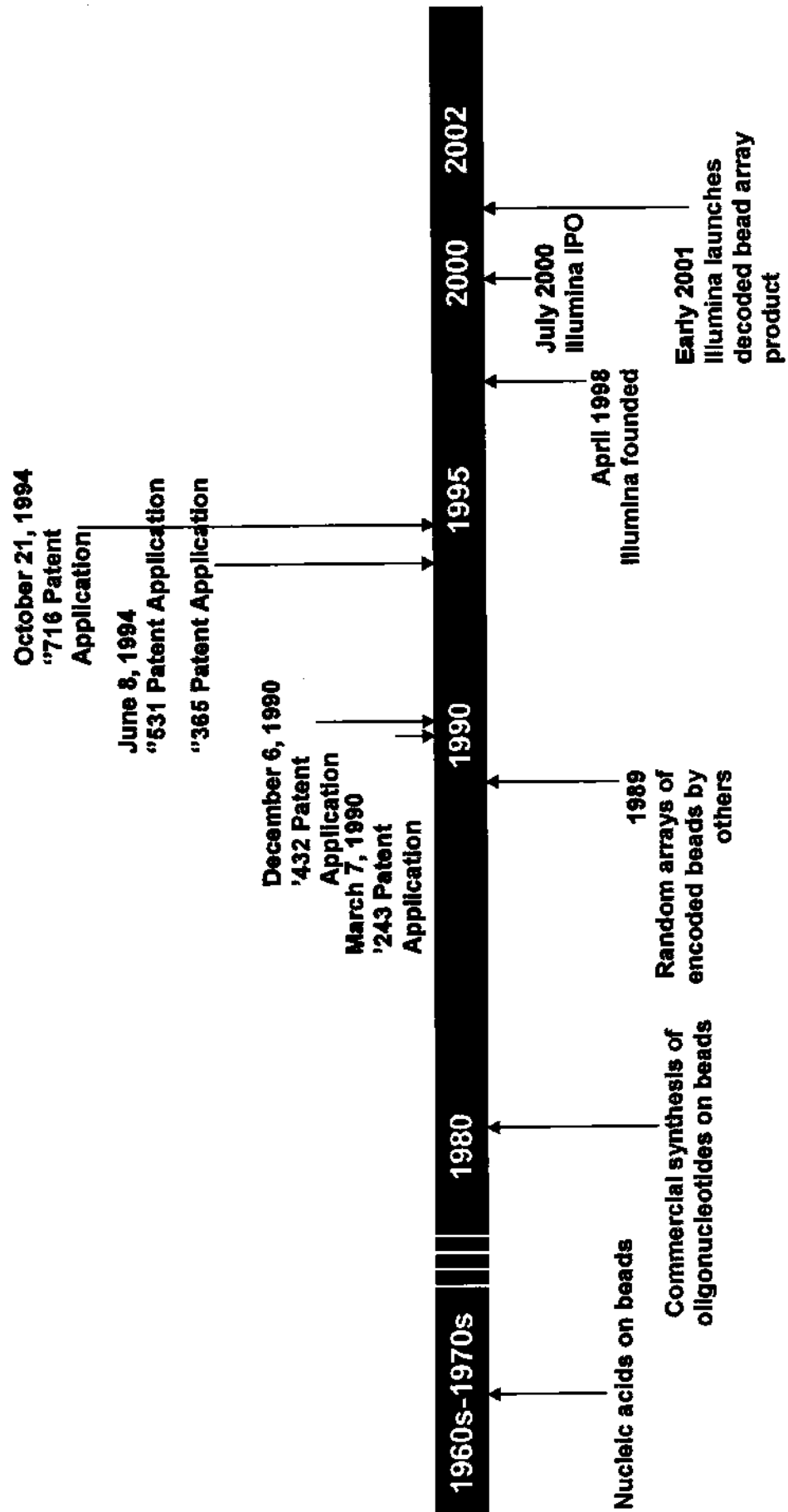
Illumina makes genotyping calls through transformation and clustering



Timeline of Applications Related to the '243 Patent



Timeline of Earliest Possible Filing of Affymetrix's Patents-In-Suit



Affymetrix's Supplemental Responses to Illumina's First Set of Interrogatories, at 5-6

Summary of Opinions

Evaluation of Patent Damages

- Reasonable royalties are appropriate

BeadArrays	4.5%	\$2,129,816
Instruments	2.0%	\$521,377
Services and research	3.0%	\$1,143,548
		\$3,794,742
(Through 2005)		

Reasonable Royalty

Overview of Analysis

- Profit apportionment
- Design alternatives
- *Georgia-Pacific* factors

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Profit Apportionment

Illumina's Profits Are Attributable to Many Factors

- Illumina's research and development
- Manufacturing processes and efficiencies
- Marketing, sales and distribution expertise
- Brand and reputation
- Other patented technology

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- Illumina's research and development
- Manufacturing processes and efficiencies
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- Brand and reputation
- **Other patented technology**

Illumina's Patents

Table of Contents

- We completed the CyView acquisition, which we believe provides us with a comprehensive approach to bead-based assays for diagnostic research and development and in-vitro and molecular diagnostic opportunities, including those involving microarrays as well as high-throughput arrays. We believe the CyView technology will be highly complementary to our existing technology and will enable us to develop new products and services for our existing customers and accommodate the development of additional technologies, products and services.
- We completed the development and launch of our Illumina whole genome genotyping solution. This family of products offers a flexible BeadChip design and high density architecture. Illumina's Whole Genome Genotyping products are based on our BeadArray technology and provide the industry's only 100% quality control with an average 30-fold feature redundancy. The technology is used in a variety of applications, including but not limited to large-scale interrogation of variation in the human genome.
- We have been exploring the commercialization of our technology in a number of other markets.

Intellectual Property

We have an extensive patent portfolio, including, as of February 1, 2006, ownership of, or exclusive licenses to, 38 issued U.S. patents and 102 pending U.S. patent applications, including six allowed applications that have not yet issued as patents, some of which derive from a common parent application. Our issued patents, which cover various aspects of our array, assay, oligo synthesis, instrument and chemical detection technologies, expire between 2011 and 2022.

Our issued patents, as to which we entered in prior years, claims or approximately \$10 million, which was recognized as revenue during the first quarter of fiscal 2005.

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Source: U.S. Patent & Trademark Office, March 2006

Affymetrix v. Illumina
C.A. No. 04-10001 JFF
Trial Exhibit
DX 1516

Source: Illumina's 10-K Form (Mar. 6, 2006)

Profit Apportionment

Tufts

- **Worldwide, exclusive license**
- **Licenses patented technology underlying Illumina's accused products**
- **3% royalty on net sales of beadarrays**

Reasonable Royalty

Overview of Analysis

- Profit apportionment
- Design alternatives
- *Georgia-Pacific* factors

Design Alternatives

Overview

- Represents a cap as to what Illumina would be willing to pay for license
- Total cost to Illumina to implement is less than \$7 million

Design Alternatives

'716 Patent

- **No conversion step (Cartesian coordinates)**
 - 2002 cost is \$75,000
- **OR**
- **Eliminate base call reporting**
 - Minimal expense because commercially used previously

Design Alternatives

'531 Patent

- One array per solid support
- 2002 cost is several million dollars

Design Alternatives

'365 Patent

- Non-barcode identification system
- 2002 cost is less than \$0.5 million

Design Alternatives

'243 Patent

- **White light with filters**
 - **2002 cost is less than \$3 million**
- OR**
- **Nanocrystals**
- OR**
- **Non-covalent attachment**
 - **2002 cost is less than \$0.5 million**

Reasonable Royalty

Overview of Analysis

- Profit apportionment
- Design alternatives
- ***Georgia-Pacific*** factors

Licenses to Comparable Patents

PHRI

- Worldwide license
- Licenses patented array technology comparable at least to the '531 patent
- 0.7% royalty rate

LICENSE AGREEMENT

This Agreement, effective on the first date specified by use of the undersigned herein, is between the PUBLIC HEALTH RESEARCH INSTITUTE of The City of New York, Inc., a not-for-profit corporation of the State of New York having laboratory facilities at 455 First Avenue, New York, NY 10018 ("PHRI") and APPLIED BIOSYSTEMS, a corporation of the State of California having offices at 3180 Central Expressway, Santa Clara, CA 95051 ("APPLIED").

RECITALS

- PHRI owns patent applications relating to oligonucleotide arrays and methods employing such arrays, as hereinafter defined.
- APPLIED's business includes developing, manufacturing and selling chips that include arrays of bound oligonucleotides and RNA containing such chips.
- APPLIED desires a worldwide exclusive license under said PHRI array patent applications and patent issuing therefrom.
- PHRI owns patent applications relating to labeled oligonucleotides referred to by PHRI as "molecular beacons" and to assays and kits employing said molecular beacons and to certain fluorescence/quantitative PCR for oligonucleotide probes.

APPLIED hereby
acknowledges
that it is
bound by
this license
DX 772

PHRI (02/01)

CONFIDENTIAL, ATTORNEY EYES ONLY

Affymetrix Changed The Algorithm For Its Genotyping Product

Algorithm and Blues New Software Enables Affy to Cut 500k Price Tag, But Investors Left Spooked... Page 2 of 2

"Affy's new software doesn't affect Affymetrix's guidance going forward. We feel very comfortable with the position of our products in the market and the pricing of those products. We don't see any direct impact."

Still, genotyping product and the company could not be reached for comment on the future of such a product.

BILL LAM

Affy had touched upon the substance of its new algorithm in May during its investor conference when Chief Financial Officer David L. Schaffman said Affy would "re-evaluate" its pricing for its Affymetrix Affymetrix products when the company released the chip last October (see [BNA's 5/29/2006](#)).

According to Schaffman, Affy's original algorithm "didn't allow the power of the array to be fully realized and as a result we were experiencing disappointing delays in scaling up to their 200k product." The added cost of the array would be in the hands of all Affy 100k customers by the end of May.

Affy has discussed a series of difficulties related to the launching of the 500k chip, among them a manufacturing problem that forced the company to remove its 137,000 guidance and a timing issue with reorders that resulted in lower than anticipated revenue for the first quarter of this year.

Schaffman pointed out to keep the problems with the company's initial algorithm had created scale-up issues for Affy customers which, in turn, affected the timing of reorders.

"When the other software came out, a larger degree of disparity between heterozygote calls and homozygote calls was evident," he said. "The new software algorithm takes the same information from the chip but with a different algorithm and produces a different result. It really has corrected the challenges we've seen in terms of the software," he said.

Schiffman pointed out in May that the problems with the company's initial algorithm had created scale-up issues for Affy customers which, in turn, affected the timing of reorders.

"[With the older software] there was a larger degree of disparity between heterozygote calls and homozygote calls," Schiffman told the investors.

<http://www.biostatsystems.com/factsheets/060504affymetrix134202-1.html#typo-yf>

Philly said "We don't see any direct impact."

Blues had not publicly discussed a timeline for releasing a 1 million

Affymetrix v. Blues
Genotyping
Trial Package
BX 1559

<http://www.biostatsystems.com/factsheets/060504affymetrix134202-1.html#typo-yf>

Source: "Algorithm And Blues New Software Enables Affy to Cut 500k Price Tag, But Investors Left Spooked," BioArray News (July 25, 2006)

Known Shortcomings in Affymetrix's Genotyping Software

Algorithms and Issues: New Software Fails: Affy - Chip To Ltd 500K Price Tag, But Inve... Page 2 of 2

"Affy's announcement doesn't offer sufficient detail to allow investors to make an informed decision about the company's ability to deliver on its promises," said a research analyst at a major investment bank. "The company's announcement is a step in the right direction, but it doesn't provide enough information to allow investors to make a decision about the company's ability to deliver on its promises."

According to the analyst, Affy's announcement "didn't allow the power of the company's technology to be fully appreciated. The company's technology is a game-changer, but the announcement didn't provide enough information to allow investors to make a decision about the company's ability to deliver on its promises."

Affy has announced a series of difficulties related to the launch of its 500K chip, among them a manufacturing problem that forced the company to revise its Q3 2005 guidance and a pricing issue that resulted in lower than anticipated revenue for the first quarter of this year.

Schellman pointed out in May that the problems with the company's initial algorithm had created a "major" issue for Affy customers. In June, he noted the timing of the problems. "The problems with the company's initial algorithm had created a 'major' issue for Affy customers. In June, he noted the timing of the problems."

"The problems with the company's initial algorithm had created a 'major' issue for Affy customers. In June, he noted the timing of the problems. The problems with the company's initial algorithm had created a 'major' issue for Affy customers. In June, he noted the timing of the problems."

"The previous algorithm tended to under-call heterozygotes, which could have introduced a bias in downstream analysis," he said.

Yes, Matus said, algorithms for

ing that,

In a conference call with investors, Barnes CEO Jay Flakley said Affy's announcement would have no effect on the company's earnings going forward.

"We had very candidly with the problem of our products in the market and the pricing of those products [see related story] [this to investors] Flakley said. "We don't see any direct impact."

Barnes has not publicly disclosed a timeline for releasing a 1-million

100 million
CA 94040
The Station
BX 1559

<http://www.bioscience.com/issue/030105/030105-1.html#p030105-1>

Source: "Algorithm And Blues: New Software Enables Affy to Cut 500k Price Tag, But Investors Left Spooked" BioArray News, July 25, 2006

Summary

Reasonable Royalties

	Rate	Royalty Base	Royalties
BeadArrays	4.5%	\$47,329,254	\$2,129,816
Instruments	2.0%	\$26,068,872	\$521,377
Services and research	3.0%	\$38,118,264	\$1,143,548
(Through 2005)			\$3,794,742

Lost Profits Is Not Appropriate

Availability of Design Alternatives

- Illumina had design alternatives available
- Competitive technologies exist for which Dr. Lynde does not properly account

Capacity Constraints

SUSAN E. SIEGEL
Highly Confidential - Attorneys' Eyes Only
March 3, 2006

Page 1

THE VIDEO OPERATOR: Back on the record.
The time is 4:08 p.m.

HO, COLLIER: Ha, Siegel, thank you very
much. I'll be back on the record.

Page 150

1 early 1998, there was some issues, and then we
2 got down some of those. But then we had so much
3 capacity because as a board we said we would always
4 have more capacity so we'd never be in those
5 manufacturing capacity constraints. So although
6 we'd have yield issues, we always had a lot of
7 capacity. That wasn't the case in the second half

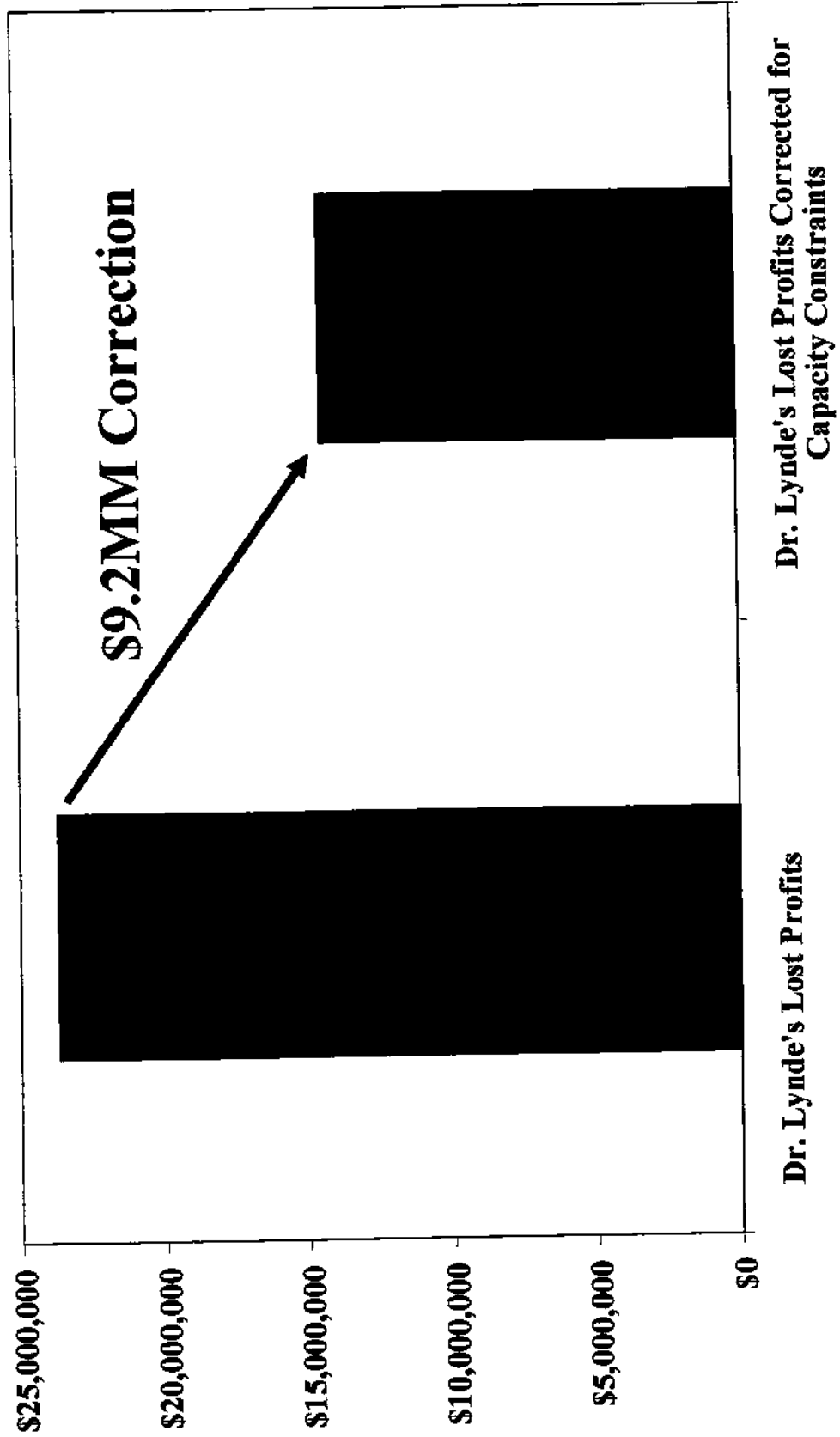
So although
we'd have yield issues, we always had a lot of
capacity. That wasn't the case in the second half
of 2005.

THE VIDEO OPERATOR: Back on the record.
The time is 4:08 p.m.
HO, COLLIER: Ha, Siegel, thank you very

Source: Siegel Dep., at 150:5-8

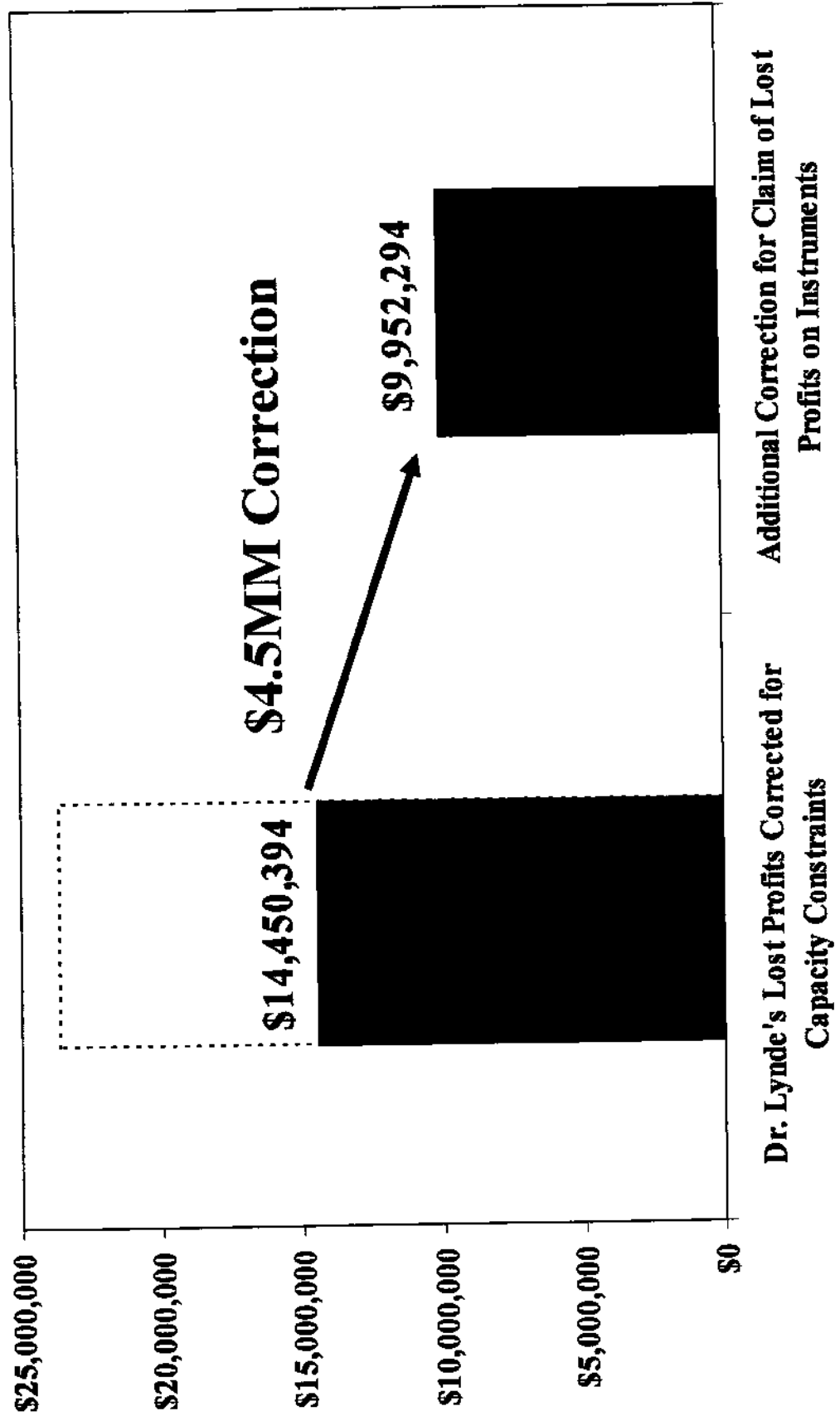
Overstates Lost Profits

Correcting for Capacity Constraints



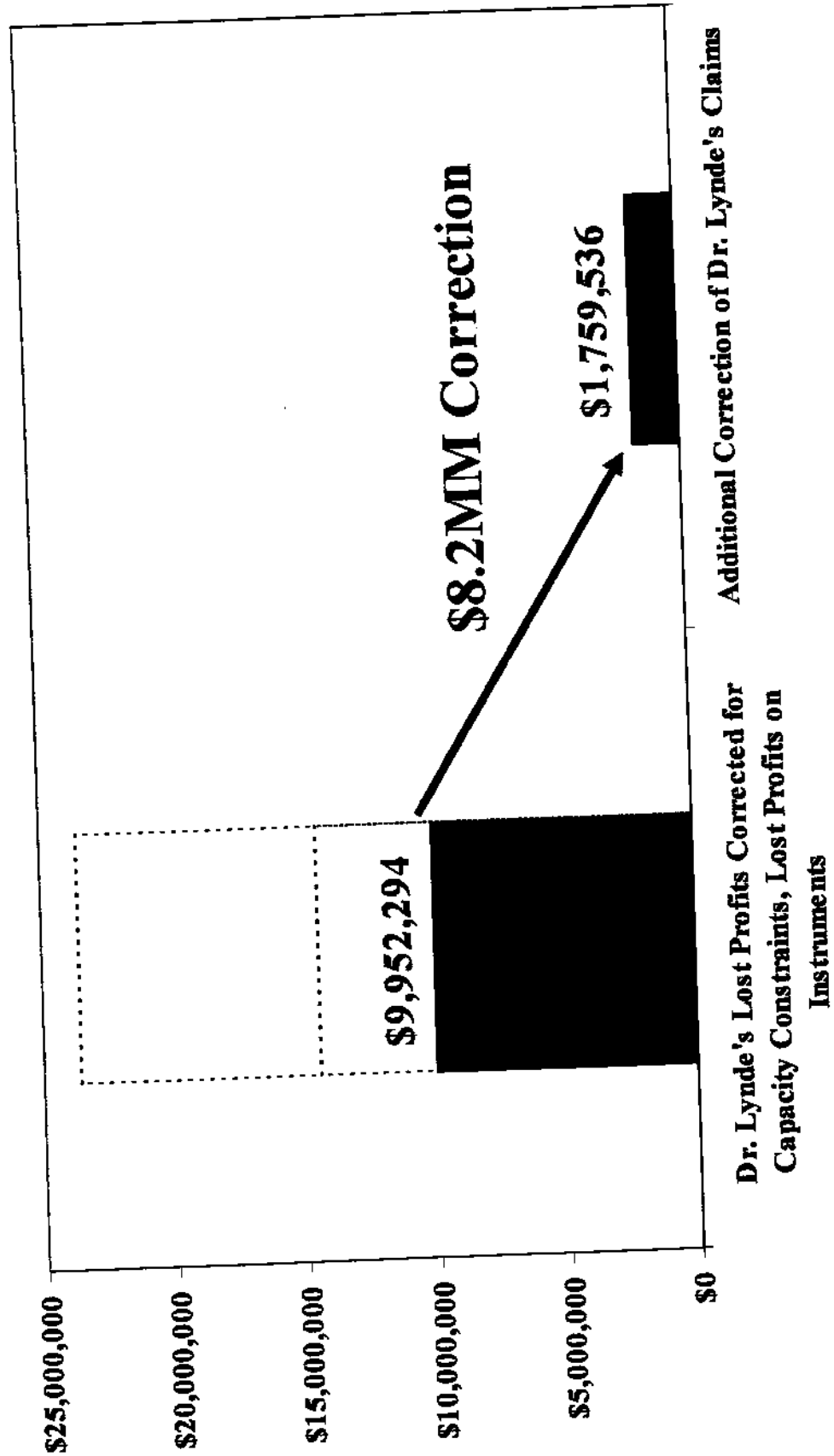
Overstates Lost Profits

Correcting for Lost Profits Claim for Instruments



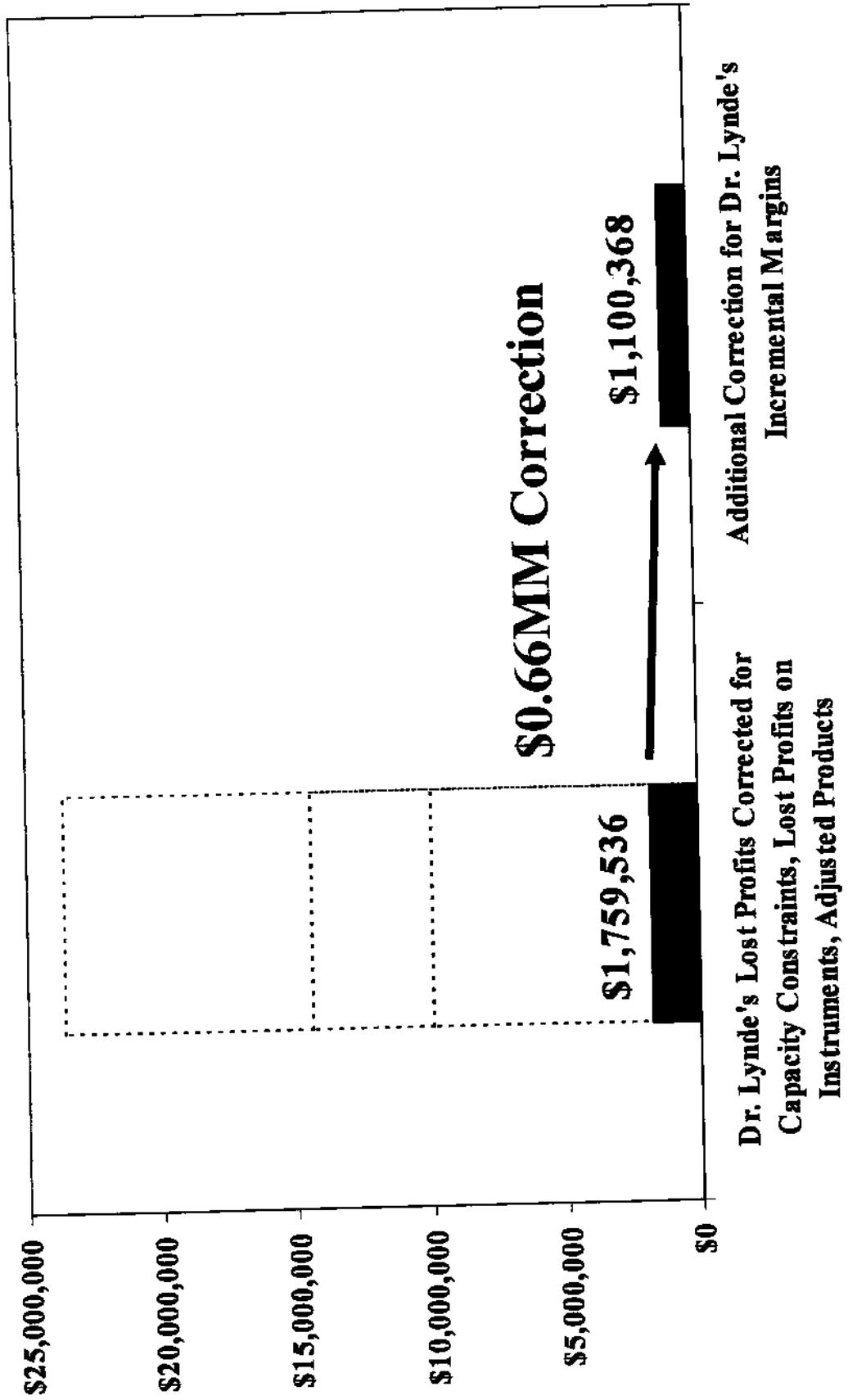
Overstates Lost Profits

Correcting for Lost Profits Claim For Incorrect Identification of Competitive Products



Overstates Lost Profits

Correcting Dr. Lynde's Incremental Margin



Overstates Lost Profits

Lost Profits Summary

- If lost profits are appropriate, corrections to Dr. Lynde's lost profits calculation are necessary
- Correcting for these errors reduces Dr. Lynde's lost profits claim by **\$22,575,632** through 2005
- Dr. Lynde's lost profits claim should be adjusted to be no more than **\$1,100,368** through 2005

Takara-Shuzo Sought to Renegotiate

'93, 11/80 PHS 1145 PLS 977 510 5110
 TAKARA SHUZO CO., LTD.
 TOKYO
 TAKARA BIO INC.
 LAKEVIEW

Given the deleterious impact that the activities of Agilent and others have had on Takara Bio's market for the past half-year or more, we do not believe that we should have an obligation to make the minimum royalty payments until such time as the activities of all non-licensees have ceased and we are able to engage in the sale of microarray products under the fair market conditions contemplated by the License Agreement.

except in the sale of microarray products under the fair market conditions contemplated by the License Agreement. Until such time, we do not feel that we will be violating the benefits of the License Agreement upon which the payment of the minimum royalty is premised. Based on the foregoing, we wish to inform you that we do not anticipate making the minimum royalty payment until 2007 and we will not be able to engage in the sale of microarray products under the fair market conditions.

2. Royalty Rate. With respect to the applicable royalty rates set forth in Table 1 and Table 2 of Article 4.2.2 of the License Agreement, and based on the number of microarray products we believe it would be fair to sell and reasonable for the applicable rate of the Royalty Fee defined in the License Agreement set forth in Table 1 with respect to sales in quantities to be sold, we have issued the following

Via E-mail
 DX 1040
 EXHIBIT
 529
 7/8/06

AVI_200408
 AVI_200408

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Overstates Reasonable Royalty Damages

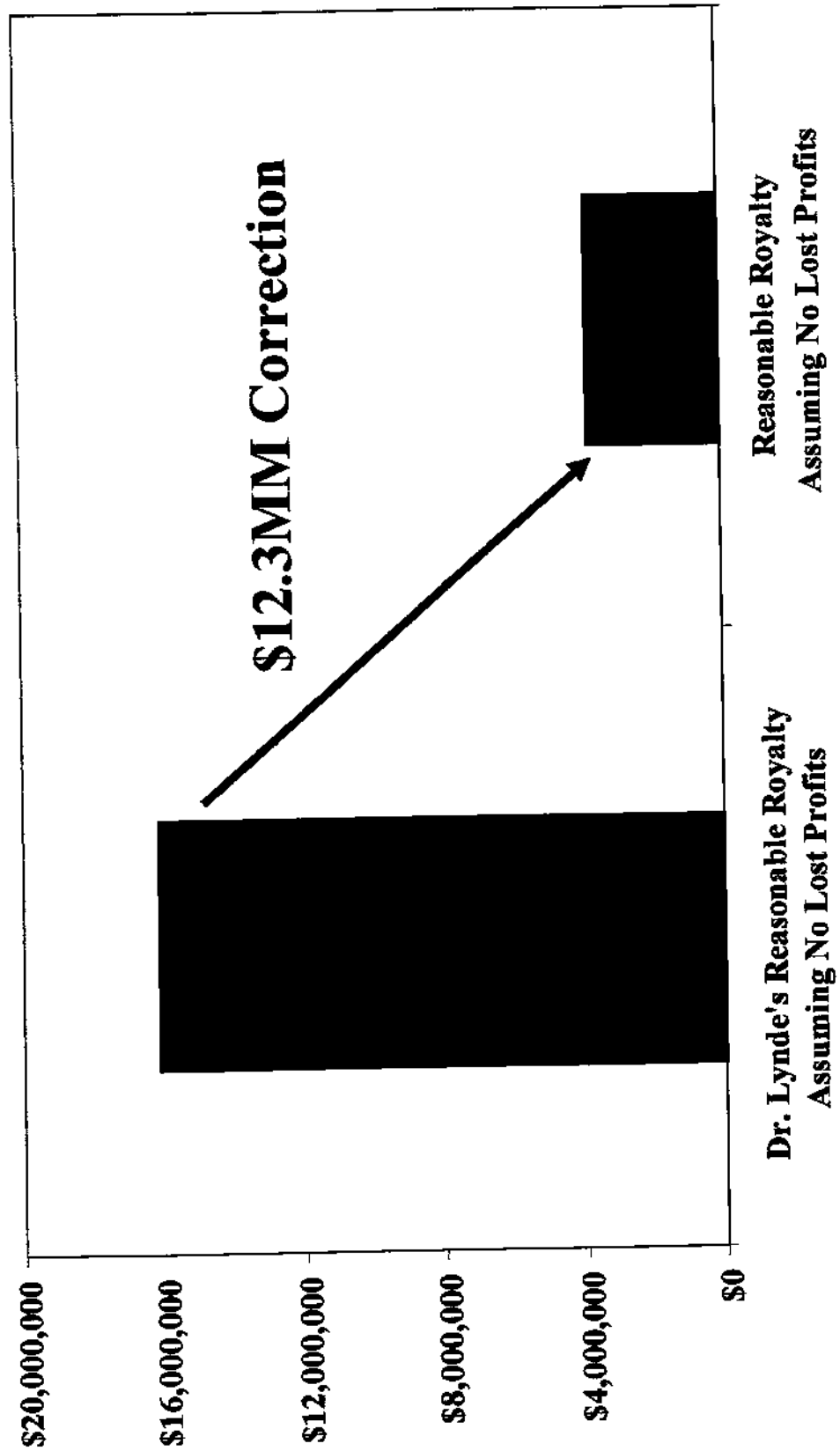
Genomic Solutions

- Does not license any of the patents-in-suit
- Licenses 155 other Affymetrix patents and patent applications
- Genomic Solutions sought to renegotiate the terms to reduce the financial burden

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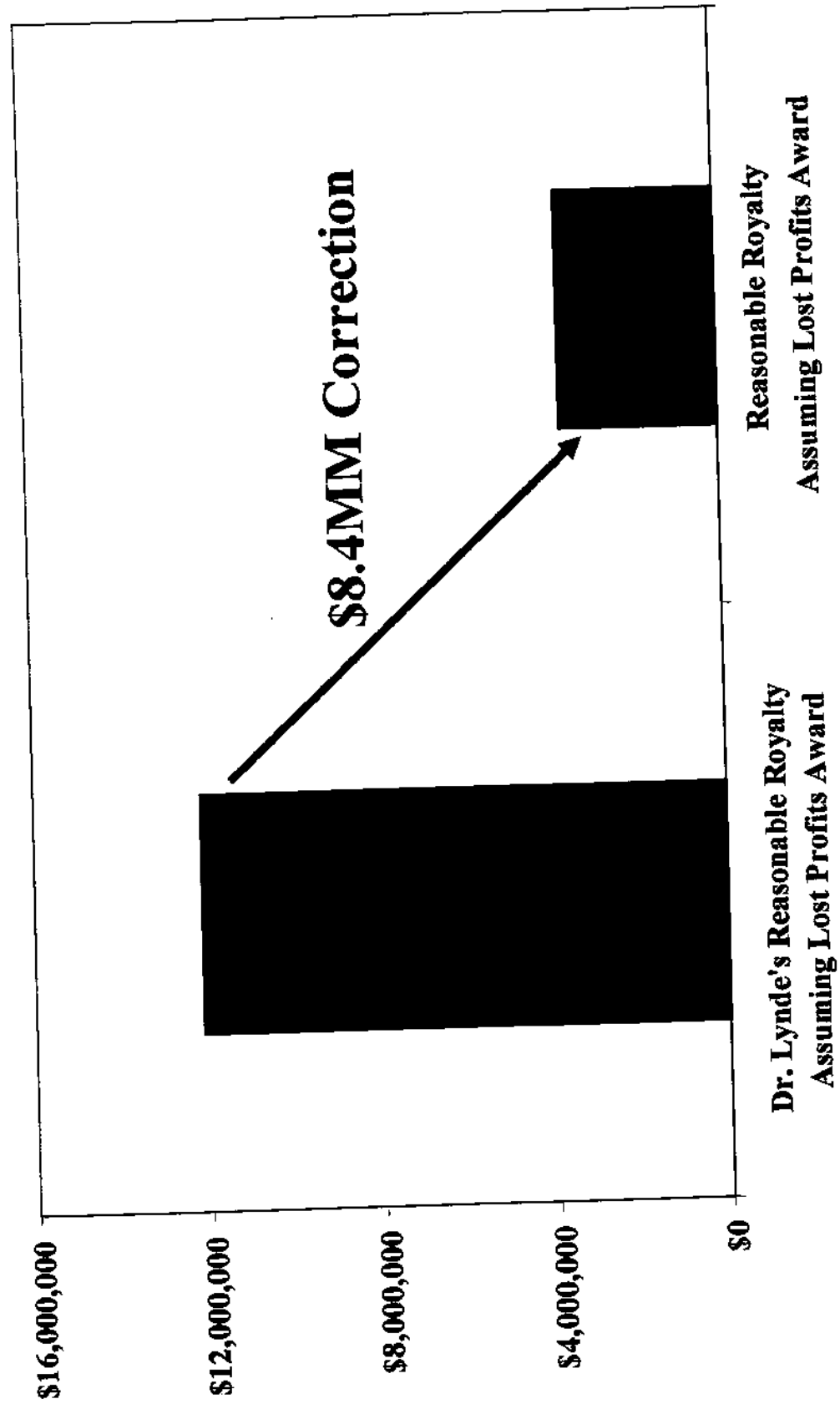
Overstates Reasonable Royalties

Reasonable Royalty Assuming No Lost Profits Award



Overstates Reasonable Royalties

Reasonable Royalty Assuming Lost Profits Award



Summary of Opinions

Evaluation of Patent Damages

	Rate	Royalties
BeadArrays	4.5%	\$2,129,816
Instruments	2.0%	\$521,377
Services and research	3.0%	\$1,143,548
		\$3,794,742

(Through 2005)